REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

In the Official Action, Claims 2, 3, 8, 10, 15, 25 and 27 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

In response, applicants have amended the claims in a manner as shown above. Specifically, applicants have provided the corresponding chemical names from the Chemical Abstracts, for the protein kinase inhibitors recited in the above-mentioned Claims. Since the amendments do not introduce any new matter into the originally filed application, entry thereof is respectfully requested. With respect to protein kinase inhibitors, such as CP-564959, ZD 2171 and CI-202, applicants submit that they are well known terms in the medical field. Therefore, a person skilled in the art would readily understand the meaning and scope of those terms.

In view of the above-described amendments, applicants respectfully submit that the instant rejection has been obviated. Therefore, reconsideration and withdrawal of the instant rejection is respectfully requested.

Furthermore, Claims 24-30 stand objected as allegedly indefinite since said claims recite a broad range as "in a mammal", and then in the same claim, it recites a narrow range as "human".

In response, applicants have amended the claims in a manner as shown above. Specifically, applicants have deleted the term "including human" in Claims 24, 26, 29 and 30. Meanwhile, applicants have added new Claims 31-34, which are dependent from Claims 24, 26, 29 and 30, to recite the limitation of "human". Since the amendments do not introduce any new matter into the originally filed application, entry thereof is respectfully requested.

In view of the above-described amendments, applicants respectfully submit that the instant rejection has been obviated. Therefore, reconsideration and withdrawal of the instant rejection is respectfully requested.

Furthermore, Claims 1-3, 5-11, 13-15 and 24-30 stand rejected under 35 U.S.C. §103(a) as obvious over Cozzi et al.(WO 98/04524) in view of Sironak et al. (Clinical Cancer Research: 2000, 6(12); 4885-4892) and further in view of Grimley et al. (US 6,274,576).

With respect to the primary reference, the Official Action avers that Cozzi et al. teaches an acryloyl distamycin compound may be combined with an antitumor agent, which includes protein kinase inhibitors. In response, applicants respectfully submit that this is simply not true. Specifically, applicants observe that Cozzi et al. discloses that a compound of formula (I) can be combined with an additional antitumor agent. See page 20, lines 6-13. Applicants further observe that Cozzi et al. disclose examples of the antitumor agents, see page 20, lines 22-29. In this regard, applicants respectfully submit that none of the antitumor agents disclosed in Cozzi et al. are protein kinase inhibitors. Therefore, the first deficiency of Cozzi et al. is that it fails to teach or suggest that a α-bromo or α-chloro- acryloyl distamycin compound of formula (I) can be combined with a protein kinase inhibitor, as described and claimed in the present application. Moreover, applicants respectfully submit that the second deficiency of Cozzi et al. is that it does not teach, disclose or suggest that an antitumor composition comprising an α-bromo or α-chloro- acryloyl distamycin compound of formula (I) and a protein kinase inhibitor having a synergistic antineoplastic effect, which is claimed in the present application.

Regarding the secondary references, for example, Sironak et al., the Official Action alleges that the motivation to combine the acryloyl distamycin compound disclosed from Cozzi et al. with ZD 1839 taught by Sironak et al. is that both compounds are taught to be useful

in treating lung cancer. The Official Action thus asserts that a person skilled in the art would have a reasonable expectation of success of combining the two compounds to produce a synergistic antineoplastic effect in the treatment of lung cancer.

In response, applicants respectfully submit that this is simply not true. Specifically, applicants submit that there would be no basis to make a generalization that if ZD 1839 and another compound are taught to be useful in treating lung cancer individually, then the combination of the two would produce a synergistic effect in the treatment of lung cancer. More specifically, applicants submit that Sironak et al. teaches that when ZD 1839 is combined with other anti-cancer agents which are useful in the treatment of lung cancer, the combined treatment leads to unpredictable results. For example, in the combination treatment against lung tumors (see page 4888. the last paragraph to page 4889, the lines before the last paragraph), while the combination of ZD 1839 with some anti-cancer agents leads to enhanced effectiveness against lung cancer tumors, the combination of ZD 1839 with GEM does not improve the activity of GEM against lung cancer tumors. Therefore, Sironak et al., by itself, rebuts the generalization that merely because ZD 1839 and another compound are useful in anti-lung-cancer treatment individually, then the combination of the two would produce a synergistic effect in the treatment of lung cancer.

Moreover, applicants submit another two scientific papers, G. Giaccone et al. (Journal of Clinical Oncology 2004, 22:777-784) and R.S. Herbst et al. (Journal of Clinical Oncology 2004, 22:785-794), enclosed as Exhibit A and B respectively, which further buttress applicant's position that no such generalization can be made that merely because ZD 1839 and another compound are useful in anti-lung-cancer treatment individually, then the combination of the two would produce a synergistic effect in the treatment of lung cancer.

Specifically, G. Giaccone et al. shows that gefitinib (Iressa, ZD 1839) in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced Non Small Lung Cancer (NSCLC) had no improved efficacy over gemcitabine and cisplatin alone. See the conclusion part at page 777. Regarding R.S. Herbst et al., it shows that gefitinib (Iressa, ZD 1839) in combination with paclitaxel and carboplatin in chemotherapy-naive patients with advanced Non Small Cell Lung Cancer (NSCLC) did not add benefit in survival, time to progression (TTP) or response rate (RR) over standard chemotherapy alone (i.e. paclitaxel and carboplatin). See the Conclusion part at page 785.

Therefore, in view of Sironak et al. and the other two publications discussed above, a person skilled in the art would arrive to a conclusion that the combination of ZD 1839 and another anti-lung cancer agent would lead to unpredictable results in the lung cancer treatment. As such, the conclusion is compelling that a person skilled in the art, would not have any reasonable expectation that the combination of ZD 1839 with a acryloyl distamycin compound, as presently claimed, would produce synergistic effect in the treatment of lung cancer.

With respect to another secondary reference, Grimley et al., the Official Action alleges that since the indole carbozoles function similarly to the acryloyl distamycin compound disclosed from Cozzi et al., (e.g. they are all used to treat cancer), a person skilled in the art would have motivation to substitute indole carbozoles by an acryloyl distamycin compound, and combine it with a protein kinase inhibitor.

In response, applicants submit that a generalization cannot be made that merely because two different compounds are useful to treat cancer individually, then a person skilled in the art would have reasonable expectation that one compound can substitute another, and be

combined with a protein kinase inhibitor to produce synergistic effect in the treatment of lung cancer. In this regard, the above remarks concerning Sironak et al. clearly demonstrate that when ZD 1839, a representative protein kinase inhibitor, is combined with other anti-lung cancer agent, the result is unpredictable in the lung cancer treatment. Applicants respectfully submit that such remarks apply equally well in this rejection, and therefore are incorporated herein by reference. As such, applicants submit that a person skilled in the art would not be motivated to combine Grimley et al. with the other two cited references in the first instance. Even combined, which is clearly not the case as discussed in the above, the combined teaching does not teach, disclose or suggest that the combination of an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I) with a protein kinase inhibitor can produce a synergistic antineoplastic effect as presently claimed.

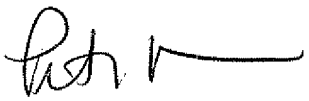
In view of the above remarks, applicants respectfully submit that Claims 1-3, 5-11, 13-15 and 24-30 are not rendered obvious by the cited references. As such, reconsideration and withdrawal of the instant rejection is respectfully requested.

Furthermore, Claims 1-3, 5-11, 13-15 and 24-30 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 of U.S. Patent No. 6,482,920 ('920) in view of Sironak et al.

Applicants observe that the '920 patent is derived from Cozzi et al. which is discussed in the above. Therefore, applicants submit that the above remarks concerning the obviousness type-double patenting rejection over Claim 1-3, 5-11, 13-15 and 24-30 in view of Cozzi et al. and Sironak et al. apply equally well to this rejection, and therefore are incorporated herein. As such, applicants submit that Claims 1-3, 5-11, 13-15 and 24-30 are not obvious over the cited references and reconsideration and withdrawal of the instant rejection is respectfully requested.

In view of foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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